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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 August 2000 (02.08.00)	
International application No. PCT/US99/27481	**Applicant's or agent's file reference** 60/109,611
International filing date (day/month/year) 19 November 1999 (19.11.99)	**Priority date** (day/month/year) 23 November 1998 (23.11.98)
Applicant DAVIS, Bonnie	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 June 2000 (21.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Diana Nissen
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RICHARDS, John
Ladas & Parry
26 West 61st Sreet
New York, NY 10023
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 03 February 2000 (03.02.00)	
Applicant's or agent's file reference 60/109,611	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/27481	International filing date (day/month/year) 19 November 1999 (19.11.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 23 November 1998 (23.11.98)
Applicant DAVIS, Bonnie	OL-282314 - Case 046522

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 Nove 1998 (23.11.98)	60/109,611	US	18 Janu 2000 (18.01.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
I. Reis

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
RICHARDS, John
Ladas & Parry
26 West 61st Sreet
New York, NY 10023
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 02 June 2000 (02.06.00)	
Applicant's or agent's file reference 60/109,611	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/27481	19 November 1999 (19.11.99)	23 November 1998 (23.11.98)

Applicant
DAVIS, Bonnie

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 June 2000 (02.06.00) under No. WO 00/30446

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

U013469-7

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 60/109,611

Box No. I TITLE OF INVENTION

DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DAVIS, Bonnie
160 Cold Spring Road
Syosset, New York 11791
United States of America

[X] This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: United States of America

State *(that is, country)* of residence: United States of America

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

[ ] applicant only

[ ] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RICHARDS, John
Ladas & Parry
26 West 61st Street
New York, New York 10023
United States of America

Telephone No. 212-708-1915

Facsimile No. 212-2468959

Teleprinter No.

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ HR Croatia
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IN India
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America ~~Continuation~~
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZA South Africa
- ☒ ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ CR Costa Rica
- ☒ DM Dominica

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

CONTINUATION OF BOX NO. IV

HANDELMAN, Joseph H. — Telephone No. 212-708-1880
GALLOWAY, Peter D. — Telephone No. 212-708-1905
CORD, Janet I. — Telephone No. 212-708-1935

Ladas & Parry
26 West 61st Street
New York, New York 10023
United States of America

BAILLIE, Iain C. — Telephone No. 089 26 90 77
MOLYNEAUX, Martyn W. — Telephone No. 089 26 90 77

Ladas & Parry
Dachauerstrasse 37
80335 Munich
Germany

CONTINUATION OF BOX NO. V

United States of America Application No. 60/109,611
Filed 23 November 1998 (23.11.98)

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 23 November 1998 (23.11.98)	60/109,611	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA/ US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	4
description (excluding sequence listing part)	:	7
claims	:	7
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	19

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Transmittal Letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

JOHN RICHARDS
AGENT FOR APPLICANTS

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid.

2. Drawings:
☐ received:
☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of [redacted] does not count as a sheet of the international [redacted]ation.

PCT

FEE CALCULATION SHEET
Annex t the Request

For receiving Office use nly

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 60/109,611

Applicant: DAVIS, Bonnie

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 240. T

2. SEARCH FEE . . . . . 700. S

'International search to be carried out by United States

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains _____ sheets.

first 30 sheets 455. b1

_____ x _____ = b2

remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B . . . . 455. B

Designation Fees

The international application contains 81 designations.

10 x 105. = 1050. D

number of designation fees payable *(maximum 10)* amount of designation fee

Add amounts entered at B and D and enter total at I . . . . . 1505. I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* separate check enclosed . . . . P

5. TOTAL FEES PAYABLE . . . . . 2445. TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify)*:

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ US

- ☐ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

12-0425 — Deposit Account No.

19 November 1999 (19.11.99) — Date *(day/month/year)*

Signature: John Richards

See Notes to the fee calculation sheet

The demand must be filed directly with the competent International Preliminary Examining Authority. If two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 60/109,611

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US99/27481	19 November 1999 (19.11.99)	23 November 1998 (23.11.98)

Title of invention: DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

DAVIS, Bonnie
160 Cold Spring Road
Syosset, New York 11791
United States of America

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
United States of America	United States of America

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US99/27481

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

RICHARDS, John
Ladas & Parry
26 West 61st Street
New York, New York 10023
United States of America

Telephone No.: 212-708-1915

Facsimile No.: 212-2468959

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description
[ ] as originally filed
[ ] as amended under Article 34

the claims
[ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes ***not to elect:***

Sheet No. 3

International application No.
PCT/US99/27481

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:		For International Preliminary Examining Authority use only: received	not received
1. translation of international application	sheets	☐	☐
2. amendments under Article 34	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	sheets	☐	☐
5. letter	sheets	☐	☐
6. other (specify)	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other (specify):

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

John Richards by David Cord
JOHN RICHARDS
AGENT FOR APPLICANT
Reg. No. 33,778

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rul 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No.	PCT/US99/27481
Applicant's or agent's file reference	60/109,611

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant
DAVIS, Bonnie

Calculation of prescribed fees

1. Preliminary examination fee	490.	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	153.	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	643. TOTAL	

Mode of Payment

☐	authorization to charge deposit account with the IPEA (see below)	☐	cash
☒	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

12-0425	21 June 2000(21.06.00)	John Richards by Agent
Deposit Account Number	Date *(day/month/year)*	Signature John Richards Reg No. 33778

4013469-7

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	13 SEP 2000
Applicant's or agent's file reference: 60/109.611 > case OL# 282314	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27481	19 NOVEMBER 1999	23 NOVEMBER 1998

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A01N 43/46 and US Cl.: 514/215, 214

Applicant
DAVIS, BONNIE

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 23 MARCH 2001

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE C. JONES Telephone No. (703) 308-1235

Form PCT/IPEA/408 (cover sheet) (July 1998)*

EM/A

ENTERED BY CENTRAL ACTION	ENTRY	TERM
JR	WO 41938	10/13/00

WRITTEN OPINION

International application No.
PCT/US99/27481

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 8-14 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US99/27481

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-40	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-40	NO
Industrial Applicability (IA)	Claims	1-40	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-40 lack an inventive step under PCT Article 33(3) as being obvious over Shapiro (U.S. Patent No. 5,668,117) in view of Conte et al. Shapiro teaches of administering acetylcholinesterase inhibitors, such as galanthamine, to treat the neurological disorder of Alzheimer's disease, (see column 4, lines 49-62). The prior art reference of Conte et al. teach the skilled artisan that there is a need for rate-controlled delivery of medication, (see columns 1 and 2 on page 1017). Clearly, it would have been obvious to one having ordinary skill in the art to employ acetylcholinesterase inhibitor, for instance galanthamine, to treat neurological disorders, such as Alzheimer's disease, with the teachings of Conte et al.

Claims 1-40 lack an inventive step under PCT Article 33(3) as being obvious over Brossi et al. (U.S. Patent No. 4,900,748) in view of Conte et al. Brossi et al. teach of the administration of inhibitors of acetylcholinesterase, like physostigmine, to treat Alzheimer's disease, (see abstract). Conte et al. disclose to the skilled artisan that there is a need for rate-controlled delivery of medication, (see columns 1 and 2 on page 1017). And so, the skilled artisan would have been motivated to simply administer an inhibitor of acetylcholinesterase in a time dependent dosage.

---------- NEW CITATIONS ----------

NONE

International application No.
PCT/US99/27481

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 60/109.611	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/27481	International filing date *(day/month/year)* 19 NOVEMBER 1999	Priority date *(day/month/year)* 23 NOVEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 43/46 and US Cl.: 514/215, 214		
Applicant DAVIS, BONNIE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21 JUNE 2000	28 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE C. JONES Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/27481

I. Basis of the rep rt

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 8-14 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/27481

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-40	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-40	NO
Industrial Applicability (IA)	Claims	1-40	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-40 lack an inventive step under PCT Article 33(3) as being obvious over Shapiro (U.S. Patent No. 5,668,117) in view of Conte et al. Shapiro teaches of administering acetylcholinesterase inhibitors, such as galanthamine, to treat the neurological disorder of Alzheimer's disease, (see column 4, lines 49-62). The prior art reference of Conte et al. teach the skilled artisan that there is a need for rate-controlled delivery of medication, (see columns 1 and 2 on page 1017). Clearly, it would have been obvious to one having ordinary skill in the art to employ acetylcholinesterase inhibitor, for instance galanthamine, to treat neurological disorders, such as Alzheimer's disease, with the teachings of Conte et al.

Claims 1-40 lack an inventive step under PCT Article 33(3) as being obvious over Brossi et al. (U.S. Patent No. 4,900,748) in view of Conte et al. Brossi et al. teach of the administration of inhibitors of acetylcholinesterase, like physostigmine, to treat Alzheimer's disease, (see abstract). Conte et al. disclose to the skilled artisan that there is a need for rate-controlled delivery of medication, (see columns 1 and 2 on page 1017). And so, the skilled artisan would have been motivated to simply administer an inhibitor of acetylcholinesterase in a time dependent dosage.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	25 JAN 2001

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
60/109.611	

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/27481	19 NOVEMBER 1999	23 NOVEMBER 1998

Applicant
DAVIS, BONNIE

JAN 29 2001

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DWAYNE C. JONES Telephone No. (703) 308-1235
Facsimile No. (703) 305-3230	

Form PCT/IPEA/416 (July 1992)*

ENTERED BY CENTRAL ACTION
ENTRY 1E TERM
45287 2/25/01

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing *(day/month/year)*	06 APR 2000
Applicant's or agent's file reference 60/109.611	**FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US99/27481	International filing date *(day/month/year)* 19 NOVEMBER 1999
Applicant DAVIS, BONNIE	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE C. JONES JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 308-1235

Form PCT/ISA/220 (July 1998)★

(See notes on accompanying sheet)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

4013469-7

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 60/109.611	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5
International application No. PCT/US99/27481	International filing date *(day/month/year)* 19 NOVEMBER 1999	(Earliest) Priority Date *(day/month/year)* 23 NOVEMBER 1998
Applicant DAVIS, BONNIE		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27481

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 43/46
US CL :514/215, 214

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/215, 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,900,748 A (BROSSI et al.) 13 February 1990, see abstract and columns 1 and 2.	1-40
Y	US 5,668,117 A (SHAPIRO) 16 September 1997, see abstract and claims 1 and 4.	1-40
Y	CONTE, U. et al. Press-coated tablets for time-programmed release of drugs. Biomaterials. 1993, Vol. 14, No. 13, pages 1017-1023, entire document.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 2000	06 APR 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DWAYNE C. JONES JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27481

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, CA, BIOSIS, USPATFULL, MEDLINE, DRUGU, TOXLINE, TOXLIT search terms include: lycoramine, galanthamine, delayed##(3a)release###, neurodegenerative(3a)disease#, alzheimer?

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(54) Title: DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS

(57) Abstract

Acetylcholinesterase inhibitors are of use for treating a variety of diseases and conditions including Alzheimer's disease. They also affect circadian rhythms. In order to optimize the use of such compounds, the present invention provides dosage forms and methods of treatment wherein an effective amount of a centrally–acting acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period. Suitable acetylcholinesterase inibitors include galanthamine, lycoramine, analogs thereof and rivastigmine.

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Dosage Formulations for Acetylcholinesterase Inhibitors

Field of the Invention

The present invention relates to dosage forms for cholinesterase inhibitors that will assist in obviating some of the undesirable side effects of use of such drugs and in methods of administering such drugs for this purpose.

Background of the Invention

Recently there has been considerable interest in the use of several drugs in this class including tacrine, donepezil, physostigmine, rivastigmine and galanthamine for the treatment of Alzheimer's disease. Cholinergic drugs are known to have an effect on the body's circadian rhythms and in U. S. Patent 5585375, I have claimed the use of galanthamine for treatment of jet lag. Although beneficial in some respects, circadian effects of cholinergic drugs may cause problems for care givers in cases where the patient is unable to take care of his or herself since it can result in the patient becoming active and needing attention during the night.

Summary of the Invention

The object of the present invention is to time the release of acetylcholinesterase-inhibiting medication so as to provide it on a suitable physiological schedule, for example to ensure that it can be taken while a patient is awake in the evening and will be acting at the time of expected awakening in the morning and to provide dosage forms suitable for this purpose.

From a first aspect, the present invention provides dosage forms of a pharmaceutical composition which comprise an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period. For example in one aspect such delay will be for a period of four to twelve hours so

that a dose may be administered to the patient in the evening and allow a night's sleep before the acetyl cholinesterase inhibitor becomes active in the morning. The duration of delay chosen will depend upon the exact way in which it is chosen to administer the drug. For example if it is intended to administer the drug with an evening meal taken at, say 6:30 in the evening a twelve hour delay may be appropriate if one wishes the drug to be active the following morning. If the desired time of administration is bed time, however, a six or seven hour delay may be more useful.

From a second aspect, the present invention provides a method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor, such as Alzheimer's disease, which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.

Detailed Description of the Invention

Acetylcholinesterase inhibitors of use in the present invention are those that have a central effect and have a medium duration of action (typically from 2 to 12 hours) for the treatment of diseases where acetylcholinesterase inhibiting activity in the brain is desired, especially in the treatment of Alzheimer's disease. Suitable acetylcholinesterase inhibitors will typically have a half life in the body of from 1 to 11 hours and once released from the dosage form will pass easily through the blood-brain barrier. The most suitable compounds for this purpose are galanthamine, lycoramine and their analogs wherein wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an

alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

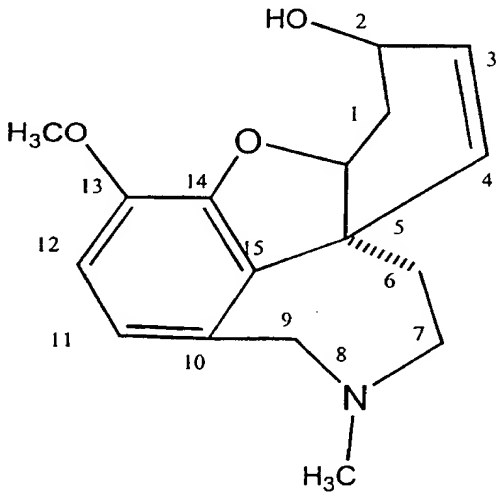
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.

When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl.

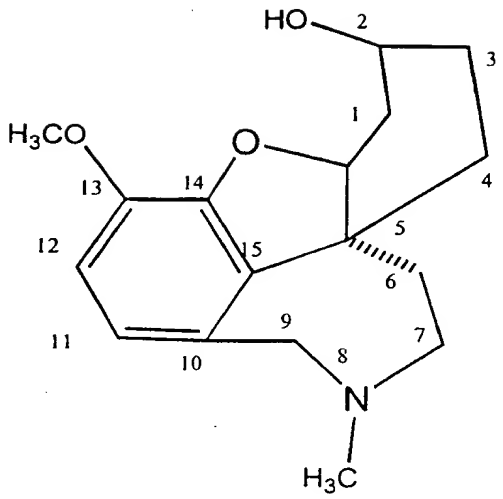
One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

Galanthamine and lycoramine have the following formulae:

Galanthamine



Lycoramine



Suitable analogs are described for example in International Patent Publication WO88/08708 and an article by Bores and Kosley in Drugs of the Future 21: 621-631 (1996). Other useful pharmacologic agents for such preparations include rivastigmine, and other pharmacologic agents with half lives of 1-11 hours.

Particularly useful analogs of galanthamine and lycoramine that are of use in the present invention include analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group, for example an alkanoyloxy or benzoyl group, of from one to seven carbon atoms or where methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from

alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Other useful analogs include compounds wherein, independently of whether or not the methoxy group has been replaced, the hydroxy group is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an acyloxy group, for example an alkanoyloxy group, typically of from 1 to 7 carbon atoms, a benzoyloxy or substituted benzoyloxy group wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups, a carbonate group or a carbamate group which may be a mono or dialkyl or an aryl carbamate or carbonate wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Although a major use of the present invention will be in the treatment of Alzheimer's disease, it is also suitable for treatment of other diseases or conditions in which there is need for increased brain acetyl choline levels after a defined period. Thus it may find use, for example for healthy persons who have need for increased acetyl choline levels some specified time in the future, for example workers changing from a day shift to a night shift or vice-versa.

In Alzheimer's disease, the primary and universal neurochemical abnormality is a deficit of acetylcholine. The normal pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep. (Kametani, 1991; Mizuno, 1991) The brain content of acetylcholine exhibits a reciprocal relationship with release patterns, presumably representing stored neurotransmitter. (Saito, 1974) Likewise, acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods. (Schiebeler, 1974) Consistent with these experimental results is the long-recognized diurnal variation of human bronchial constriction from acetylcholine inhalation, being most sensitive in the evening,

when endogenous cholinergic activity would be expected to be low, and least sensitive during waking hours, when cholinergic systems would be expected to be active (Reinberg, 1974) Humans are also sensitive to the systemic administration of the acetylcholinesterase inhibitors, physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low. These disturb sleep and produce awakenings. (Sitaram, 1979, Reimann, 1994)

Animals who are made hypocholinergic either by disruption of the high affinity choline uptake system or by being raised on a false cholinergic neurotransmitter have a reduced circadian variation of acetylcholine and a disrupted diurnal rhythm of locomotor activity, which
correlates with the cholinergic hypoactivity. (Morley 1989, Szymusiak, 1993) This same situation exists in Alzheimer patients who have both cholinergic deficits and disruption of normal sleep-wake cycles. It is of major practical importance because a patient who requires twenty-four hour supervision wears out a single caretaker, requiring multiple shifts of caretakers, or institutionalization, which is expensive, frightening to the patient, and sad for the family. (see New York Times article, July 27, 1998) An additional potential utility of a dosage form which can be taken when convenient, and active when needed, would therefore be the superimposition of a physiological rhythm of cholinergic activity, via a pill, onto a brain in which the cholinergic system is deteriorating.

Preparations for treatment of Alzheimer's disease, containing cholinomimetic agents, may stimulate intestinal peristalsis as they are released, thus promoting their own passage through the gastrointestinal tract. In may therefore be useful to incorporate into the dosage unit, or to manufacture a second, similarly timed tablet, to deliver an anticholinergic agent designed to remain outside the blood brain barrier, in order to reduce gastrointestinal motility. The anticholinergic tablet might contain, for example, probanthine, 7.5-60 mg, or robinul 1 to 8 mg. A desirable formulation for an Alzheimer patient for whom sleeping hours of 11 pm to 7 am are desirable might be a pill which could be taken at bedtime and begin to release galanthamine at 5 am at a rate of 3 mg (measured as base) per hour for 4 hours, or 2 mg/hour for 6 hours beginning at 4 am. The same pill, taken at 7 am, would cover the daytime hours.

This should allow the central nervous system to become relatively hypocholinergic at the time of desired sleep, as the half life of galanthamine has been reported to be 4.5-8 hours. (Thomsen, 1990)

Alternatively, a single pill may deliver a full day's medication, although there is some risk of dumping an excessive dose, which could be dangerous in the case of cholinergic medications. The delay before release of active medication could be chosen between one and 11 hours depending on whether the pill is to be taken at dinner or bedtime.

Likely pharmacologic agents for such preparations include galanthamine, rivastigmine, and other pharmacologic agents with half lives of 1-11 hours. Dosage units for twice daily administration should contain from 4-16 mg of galanthamine (as base), or 2-10 mg of rivastigmine, both of which should be doubled in the case of once per day dosage units. Dosages for other suitable agents can be determined by standard techniques such as those set out for example in Chapter 6 (by Benjamin Calesnick) of Drill's Pharmacology in Medicine (Fourth Edition Joseph R DiPalma ed, McGraw-Hill 1971 or in Chapter 6 (by B. E. Rodda et al) of Biopharmaceutical Statistics for Drug Development (ed. Karl E. Peace, Marcel Dekker Inc, 1988). Anticholinergic agents, if needed, could be probanthine, 7.5-60 mg, to be delivered at the same time as the cholinomimetic agents, or robinul (1 to 8 mg) or similar agents incorporated so that a typical dose is delivered within the time frame of the cholinomimetic release.

Delayed action formulations for use in the present invention typically are those used for oral administration and include tablets, capsules, caplets and other convenient devices. Such dosage units may be prepared by methods well known to those skilled in the art, such as those described in Sustained Release Medications by J.C. Johnson, Noyes Data Corporation, 1980, and an article by Conte et al in Biomaterials 1993 vol 14 pages 1017 to 1023 entitled Press-coated tablets for time-programmed release of drugs, both of which are incorporated herein by reference. For example the active compounds may be coated or incorporated in a matrix which controls the elapse of between administration of the dose and the time at which release is desired.

What I claim is:

1. A dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period.

2. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.

3 A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.

4. A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.

5. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.

6. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours

7 A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein the methoxy group thereof is replaced by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

8. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

9. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the N-methyl group of galanthamine or lycoramine is replaced by hydrogen, alkyl, benzyl or a cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.

10. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

11 A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms

12. A dosage from as claimed in claim 11 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

13. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group

wherein the alkyl groups contain from 1 to 8 carbon atoms.

14. A dosage from as claimed in claim 12 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

15 A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

16 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

17 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.

18 A dosage form of a pharmaceutical composition as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

19. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is galanthamine.

20. A dosage form as claimed in claim 1 wherein said acetylcholinesterase inhibitor is rivastigmine.

21. A method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.

22. A method of treatment as claimed in claim 21 wherein said patient is suffering from Alzheimer's disease.

23 A method of treatment as claimed in claim 21 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.

24 A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.

25. A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.

26 A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.

27. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours

28 A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

29. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

30 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

31. A method of treatment as claimed in claim 30 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

32. A method of treatment as claimed in claim 31 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

33. A method of treatment as claimed in claim 32 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

34 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

35 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

36 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.

37. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is galanthamine.

38. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is rivastigmine.

39. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is administered in conjunction with a compound that reduces its peripheral effects.

40. A method of treatment as claimed in claim 39 wherein said acetylcholinesterase inhibitor is administered in conjunction with a suitable dose of probanthine or robinul.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27481

A. CLASSIFICATION OF SUBJECT MATTER

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US CL :514/215, 214

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/215, 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	CONTE, U. et al. Press-coated tablets for time-programmed release of drugs. Biomaterials. 1993, Vol. 14, No. 13, pages 1017-1023, entire document.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, CA, BIOSIS, USPATFULL, MEDLINE, DRUGU, TOXLINE, TOXLIT search terms include: lycoramine, galanthamine, delayed##(3a)release###, neurodegenerative(3a)disease#, alzheimer?